

REMARKS

Applicants provide the foregoing amendments and following remarks in response to the Office Action dated June 27, 2008, hereinafter, "the Office Action".

Claims 32-36 are amended herein. Claims 42-45 are newly added. Applicants respectfully request entry of the amendments and new claims, which add no new matter. The amendment to claim 32 finds support for example, at least on page 5, paragraph [0026], as well as well as in Example 3 (including Table 3). Amendments to claims 33-36 are to make the language of the claims conform to that of amended claim 32, from which they depend. New claims 42-45 are supported at least in paragraph [0026] on page 7, and in Example 7 (including Table 20) and Example 8 (including Tables 23, 24, 25, and 26).

Upon entry of the amendments, claims 32-45 will be pending. Applicants respectfully request reconsideration of the application in view of the following remarks.

Rejections under 35 U.S.C. §103

Seilhamer et al., Nitta et al., and Kelley et al.

I. Applicants respectfully traverse the rejection of claims 32 and 37-41 under 35 U.S.C. § 103(a) as allegedly being obvious over Seilhamer *et al.*, U.S. Patent 6,897,030, in view of Nitta *et al.*, *Am. J. Nephrol.* 18: 411-15, 1998, and in further view of Kelley *et al.*, *Quart. J. Med.* 92: 295-97, 1999.

As stated in the MPEP [2143]:

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.

The Supreme Court further emphasized the need for providing a reasoned argument for obviousness in *KSR International Co. v. Teleflex Inc.*, by citing *in re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006)): "Rejections based on obviousness grounds cannot be sustained by mere

conclusory statements; instead, there must be some rational underpinning to support the legal conclusion of obviousness.”

The claimed invention is drawn to a method of determining the occurrence or nonoccurrence of an ischemic stroke in a subject. In these methods, an assay is performed by contacting a sample of bodily fluid from the subject with an antibody that binds the 108 amino acid brain natriuretic peptide (BNP) precursor or one or more markers related thereto, such as BNP or NT-proBNP. The results of this assay are then used to determine the occurrence or nonoccurrence of an ischemic stroke in the subject.

The obviousness rejection cites (1) Seilhamer *et al.* for disclosing immunoassays for detecting BNP; (2) Nitta *et al.* for disclosing that in hemodialysis patients, a higher level of BNP is found in patient having a low ejection fraction, characteristic of left ventricular function (LVSD); and (3) Kelley *et al.* for disclosing that asymptomatic LVSD may be found in *some* patients who have had a stroke. Based on these disclosures, the Office Action states that it would have been *prima facie* obvious to use a BNP assay to evaluate stroke (Office Action, page 5).

Applicants disagree. Applicants assert that the references, alone or in combination, fail to provide any teaching, suggestion, motivation, or a basis for any rationale for performing an assay to detect BNP in a sample of a subject and using the results of the assay to determine the occurrence or nonoccurrence of ischemic stroke in the subject. Applicants assert that no *prima facie* case for obviousness based on the cited references has been made.

The cited references do not disclose determining the occurrence or nonoccurrence of ischemic stroke, and do not disclose correlating the presence or amount of BNP with the occurrence or nonoccurrence of ischemic stroke, as provided in independent claim 32. Kelly *et al.* is the only cited reference that mentions stroke in any context. The Office Action quotes Kelly *et al.* (page 296, first column): “One might expect that about 10-35% of stroke/TIA/PVD patients have asymptomatic LVSD”. Applicants point out that in Kelly *et al.* “stroke/TIA/PVD patients” means, in aggregate, stroke patients, patients that have experienced transient ischemic attacks, and patients having peripheral vascular disease (see Kelly *et al.*, page 295, first column, second paragraph). Thus, Kelly *et al.* provides that taking stroke, TIA, and PVD patients together, some 10-35% of the group “might be expected to have LVSD”. Kelly *et al.* further

provides that the underlying study on stroke (Kelly *et al.*, page 295, second column, second paragraph) that found that 10 out of 102 stroke patients --that is, only about one in ten -- had LVSD. (In the only other study quoted in Kelly *et al.* that used stroke patients, 27% of stroke patients *with coronary artery disease* had LVSD [page 295, second column, second paragraph].)

Nitta *et al.* also fails to provide any reason for assuming BNP to be correlated in any way with any type of stroke. Nitta *et al.* discloses that the mean plasma BNP level was lower in hemodialysis patients that had a low ejection fraction (EF). Based on the teachings of Nitta *et al.*, and even assuming that the correlation of BNP level with low EF/LVSD in hemodialysis patients as disclosed in Nitta *et al.* is representative of the relationship between BNP level with LVSD in general, one of average skill in the art would have no rational basis for using an assay for BNP to determine the occurrence or nonoccurrence of stroke. One of average skill in the art would more reasonably infer from Nitta *et al.* in combination with Kelly *et al.* that perhaps (e.g., assuming no confounding factors influencing BNP levels in the stroke population), a small minority -- approximately 10% -- of stroke patients (those having LVSD) would demonstrate an elevated level of BNP. Based on that expectation, one of skill in the art would have no rational basis for using BNP assays in the diagnosis of ischemic stroke.

The statement provided in the Office Action (page 5) that based on the teachings of Kelly *et al.*: “(t)he measurement of BNP may reduce the number of patients needing echocardiograms, aide in identifying and treating LVSD to reduce the incidence of cardiac death”, has no relevance for *determining the occurrence or nonoccurrence of an ischemic stroke*, as provided in the claims, and certainly provides no rational basis for using BNP in the diagnosis of ischemic stroke. No correlation between stroke and BNP is found in the references, and no teaching, motivation, suggestion, or rational basis is present for detecting the presence or amount of BNP to determine the occurrence or nonoccurrence of ischemic stroke in a subject, as provided in independent claim 32.

The absence of rational underpinnings to support a conclusion of obviousness is inconsistent with the requirements of a rejection under 35 U.S.C. § 103(a). In view of the foregoing, Applicants respectfully submit that no case for obviousness of claim 32, and claims

37-42 that depend from claim 32, has been made. Applicants therefore respectfully request that the rejection of claims 32 and 37-41 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Seilhamer et al., Nitta et al., Kelly et al., and Jackowski et al.

II. Applicants respectfully traverse the rejection of claims 33 and 36 under 35 U.S.C. § 103(a) as allegedly being obvious over Seilhamer *et al.*, in view of Nitta *et al.*, in further view of Kelley *et al.*, and in further view of Jackowski *et al.*, WO00/52476.

The lack of a basis for obviousness with regard to Seilhamer *et al.*, Nitta *et al.*, and Kelley *et al.* are discussed above. Jackowski *et al.* does not cure the flaws in the case for obviousness. While Jackowski *et al.* is directed to methods for assessing stroke, Jackowski *et al.* does not teach or suggest the 108 amino acid brain natriuretic peptide (BNP) precursor or one or more markers related thereto, such as BNP or NT-proBNP, can be used to determine the occurrence or nonoccurrence of ischemic stroke. As discussed in the response to the rejection above, no rationale is provided for making the combination. In view of the foregoing, Applicants respectfully submit that no case for obviousness has been established, and request that the rejection be reconsidered and withdrawn.

Seilhamer et al., Nitta et al., Kelly et al., and Velier et al.

III. Applicants respectfully traverse the rejection of claims 34 and 35 under 35 U.S.C. § 103(a) as allegedly being obvious over Seilhamer *et al.*, in view of Nitta *et al.*, in further view of Kelley *et al.*, and in further view of Velier *et al.*.

The lack of a basis for obviousness with regard to Seilhamer *et al.*, Nitta *et al.*, and Kelly *et al.* is discussed in the response above. Velier *et al.*, in disclosing caspase-3 in brain injury, does not provide any rational basis for the alleged obviousness of determining the occurrence or nonoccurrence of ischemic stroke using the results of a BNP assay, as required by claim 32, from which claims 34 and 35 depend. As discussed in the response to the rejection above, no rationale is provided for making the combination. In view of the foregoing, Applicants respectfully submit that no case for obviousness has been established, and request that the rejection be reconsidered and withdrawn.

Obviousness-type double patenting

Claims 32-41 have been provisionally rejected under the judicially-created doctrine of obviousness-type double patenting with respect to claims 68-74 of copending application 10/371,149. Applicants request that provisional obviousness-type double patenting rejections be held in abeyance until the claims as amended herein have been examined and all other rejections have been overcome.

Applicants further note that no terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. See MPEP § 804 (I)(B) (The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.).

In the event that other rejections of the present claims are successfully overcome by the current communication, withdrawal of the provisional rejections based on pending applications would be appropriate.

CONCLUSION

Applicant respectfully submits that all rejections and objections have been obviated or overcome and that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for an additional action.

Applicants are filing concurrently with these amendments and remarks a Petition for Extension of Time with the required fee. The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application, or credit any overpayment, to Deposit Account No. 23-2415.

Respectfully submitted,

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